LETTERS *to the Editor*

Drug Interactions

To the Editor: The excellent review article by Morelli and Melmon in CALIFORNIA MEDICINE 109:380-389, Nov., 1968, on "The Clinician's Approach to Drug Interaction" calls attention to some often-overlooked aspects of polypharmacy. In such a comprehensive review within limited space, it is probably inevitable that at least one error should be found; this "letter to the editor" calls attention to one.

The authors say ". . . indomethacin may cause bleeding in patients taking coumarin anticoagulants." The reference given to justify this statement (Hoffbrand and Kininmouth, Brit. Med. J. 2: 838-839, 1967) specifically states that the patient described therein developed hemorrhagic complications while on phenylbutazone and not "while taking indomethacin." The British authors nevertheless reasoned—by analogy with phenylbutazone —that indomethacin *might* produce a similar effect.

The folly of reasoning by analogy is seen by further examination of the literature; the possibility of interaction between indomethacin and anticoagulants has occurred to others, and several publications exist, specifically devoted to investigation of the effects of indomethacin in patients on anticoagulant therapy. Müller and Zollinger in "Die Entzündung — Grundlagen und Pharmakolische Beeinflussung" (a symposium volume published by Urban & Schwarzenberg, Munich, Berlin, Vienna, 1966) compared 14 patients on oral anticoagulants with indomethacin with 14 patients on the same anticoagulants without indomethacin. They concluded (freely translated): "Indomethacin may be given without any further precautions to patients on anticoagulants."

Identical conclusions were reached by Frost and Hess (in the same volume), by Müller and Herrmann, Medizinische Welt 17:1553-1554, 1966, and by Gáspárdy, Balint and Gáspárdy, Zeitschr. für Rheumaforschung 26:332-335, 1967. No contrary results by any clinician who has actually tried indomethacin in patients on anticoagulant therapy have come to my attention.

The regrettable thing about unsupported statements is that they become perpetuated in the literature, and the corrections never quite catch up with the errors. So maybe it is inevitable that the statement made in the review will be added to the already formidable list of misconceptions — many of them unfavorable — about this particular drug.

Incidentally, Morelli and Melmon omitted mention of indomethacin in their list of drugs, Appendix B, supposedly listing all generic and trade names mentioned in their review.

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The Author Replies

Professor Winter is quite correct that the evidence attributing hemorrhagic complications to combined therapy with coumarin anticoagulants and indomethacin is tenuous, at least on the basis of direct interactions. The authors would maintain, however, that circumspection would be appropriate when administering anticoagulants to a patient receiving a drug reported to cause gastrointestinal bleeding. Perhaps in this context the attribution is not entirely inappropriate in an article designed to emphasize the multiplicity of drugs and potential mechanisms of direct and indirect interaction of potential clinical importance. We

do regret any misleading implications our statement may have.

Thank you for permitting us to review Professor Winter's letter. We are grateful for his comments.

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Anti-Rh Immune Globulin: How Should We Use It?

To the Editor: A few months ago a reliable pharmaceutical house put on the market a potent preparation of anti-Rh_0 (D) gamma globulin (IgG) for the prevention of Rh immunization by pregnancy.* Many independent studies have demonstrated that 1 ml (300 mcg) of this material, given intramuscularly to an Rh negative woman within 72 hours after she delivers an Rh positive child, almost invariably prevents primary immunization to the Rh factor. It now seems clear that widespread use of such material will eventually all but wipe out hemolytic disease of the newborn due to Rh incompatibility.

Almost immediately following the appearance of this new product, the legal counsel of the California Hospital Association issued a warning to all member hospitals and their staffs that the failure of a physician to provide such treatment may leave him open to suit. Further, he urged that patients who refuse this treatment for any reason be asked to sign a legal waiver, the facts being documented in the hospital record. His statement implied strongly that this agent has thoroughly proven itself, and that no further research is needed.

As a matter of fact, the indications for the use of Rh immunoglobulin, and the correct dose under various conditions, remain by no means clear. For instance, neither the counsel's statement nor the brochure distributed with the immunoglobulin refers to ABO group of mother and child, although it is widely known that ABO compatibility plays a crucial role in the mechanism of Rh immunization, and in spite of the fact that only ABO compatible pregnancies were included in the experimental studies on this new product. Levine[1] in 1943 reported that group O, Rh negative women with group AB, Rh positive husbands almost never develop Rh antibodies due to pregnancies alone, presumably because their fetuses are all of *incompatible* ABO group. Prokop[2] failed to stimulate the production of Rh antibodies in Rh negative volunteers by injecting Rh positive blood of incompatible ABO group. Stern et al,[3,4] in a similar experiment, found a few such volunteers who did develop Rh antibodies, but the percentage was small, and the antibodies invariably of low titer. Furthermore, they injected much larger volumes of Rh positive blood than normally reach the maternal circulation during pregnancy and delivery. The question as to whether Rh negative women are *ever* immunized against the Rh factor by *uncomplicated* ABO incompatible pregnancies must remain in some doubt.

On the other hand, 1 ml of anti-Rh immune globulin may at times prove entirely inadequate. Woodrow[5] and his colleagues in Great Britain demonstrated that the likelihood of Rh immunization in ABO compatible pregnancies is directly proportional to the amount of fetal blood reaching the maternal circulation. There are at least two reports[6,7] of five Rh negative women who promptly developed Rh antibodies after delivering an Rh positive baby in spite of receiving injections of more than the recommended 300 mcg of immunoglobulin. Failure of the globulin to prevent immunization was presumably due to the very much larger than normal amounts of fetal blood in the circulation of these women, ranging in estimated volume from 60 to 350 ml. Woodrow et al[8] estimate that in one of every 300 deliveries, transplacental hemorrhage of over 100 ml occurs. Correspondingly, the British group has redesigned their study on the basis of Kleihauer tests of the mothers' blood after delivery, giving 1 ml of anti-Rh immunoglobulin when there is evidence of a fetal-maternal bleed of less than 0.25 ml, and giving 5 ml in case of larger fetal hemorrhage.

It is obviously much too early, therefore, to lay down, under threat of legal action, blanket rules regarding the use of Rh immunoglobulin in the prevention of Rh immunization. Rules of thumb, such as those issued by the manufacturer should serve only as a guide. Only after much more research and observation will the indications for this

*RhoGAM®, Ortho Pharmaceutical Corp., Raritan, New Jersey.